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(56) Documents Cited:
WO 2006/072596 A1 **WO 2005/014479 A2**
WO 2004/056369 A1
Journal of Pharmacology and Experimental Therapeutics, 2007, Vol. 321(3), pages 1032-1045.

(58) Field of Search:
Other: **CAS ONLINE**

(54) Abstract Title: **Polymorphic form of 6-(3-cyclobuty1-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-N-methyl-nicotinam ide hydrochloride for use in therapy**

(57) A polymorphic form of 6-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-N-methyl-nicotinamide hydrochloride is characterised by one or both of the following:

- an X-ray powder diffraction spectrum comprising peaks at 5% or greater relative intensity of °2θ = 4.6 and 9.2 (corresponding to lattice spacings of 19.2 Å and 9.6 Å respectively)
- an onset of melting in the range 233-240°C, as measured by DSC.

The polymorph may be prepared by treating a solution of the free base, 6-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-N-methyl-nicotinamide, in methanol with one equivalent of a chloride source (such as acetyl chloride or HCl), followed by crystallisation with at least 1.5 volumes of ethyl acetate.

The polymorph may be used in medicine to treat neurological, psychiatric, sleep and gastrointestinal disorders, pain, epilepsy and obesity.

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Figure 1: X-Ray Powder Diffraction Pattern of the Polymorph

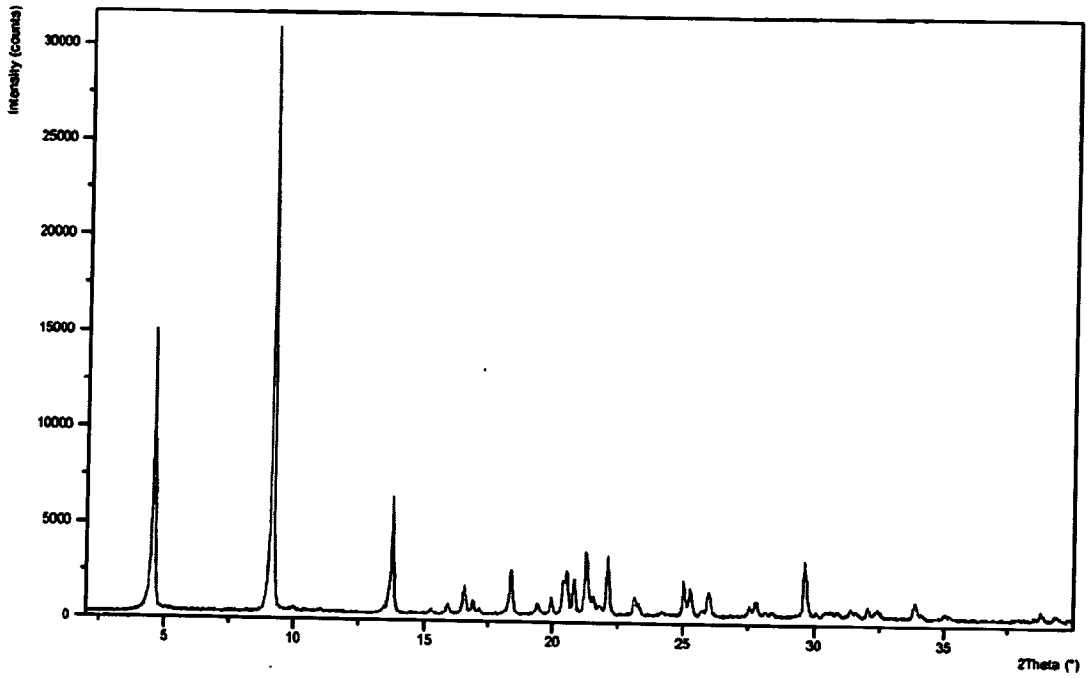


Figure 2: DSC thermogram of the Polymorph

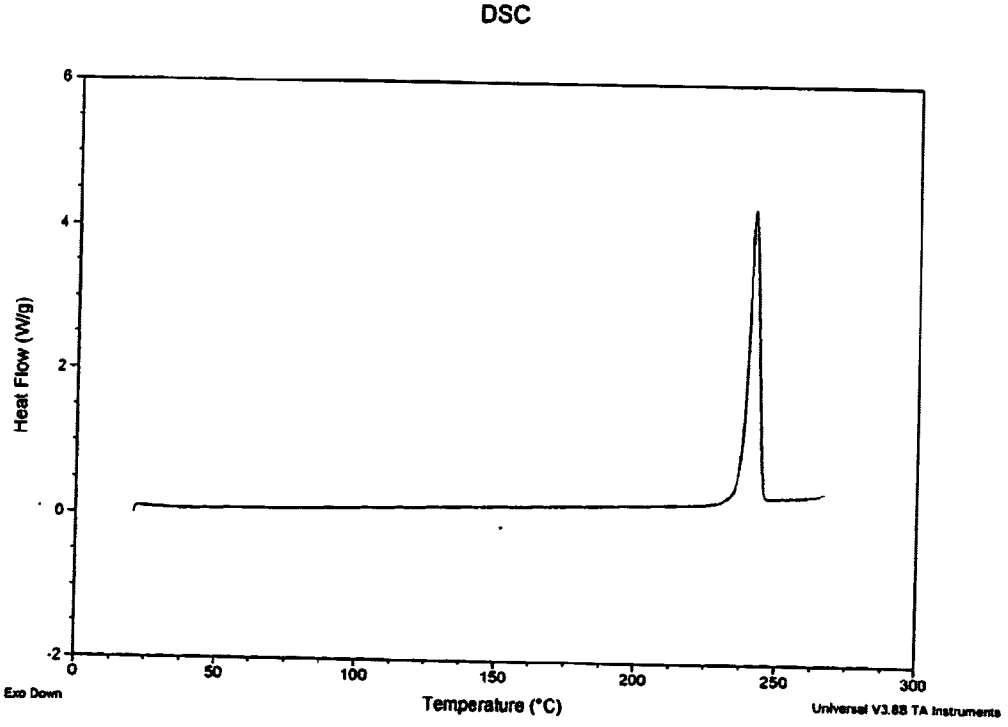
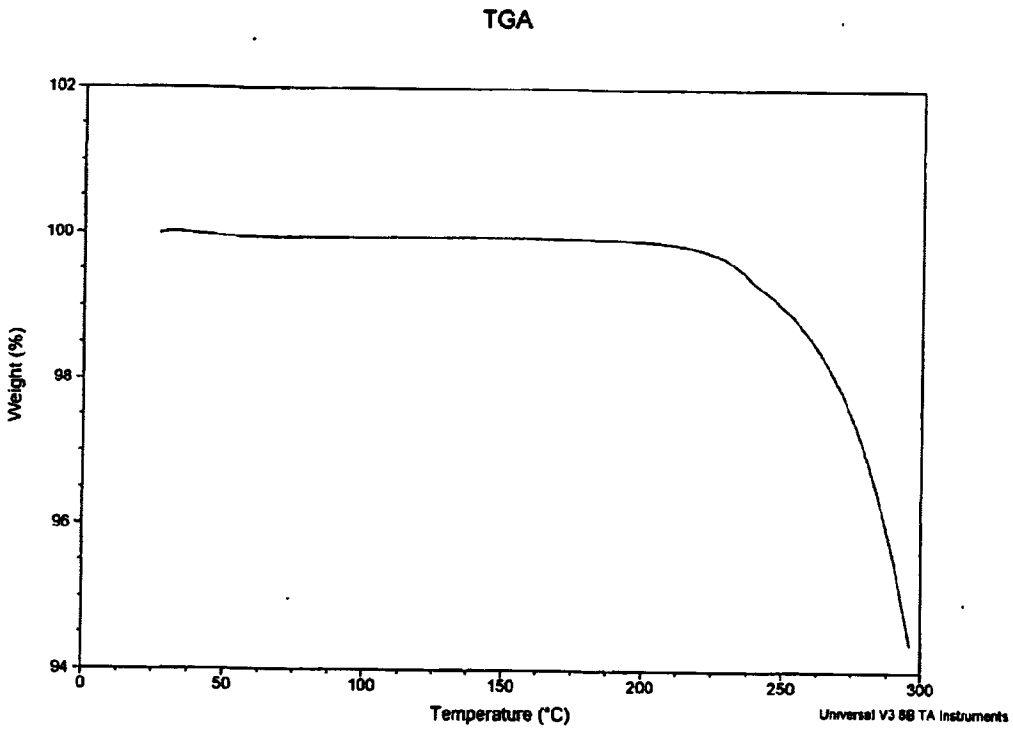


Figure 3: TGA thermogram of the Polymorph



NOVEL PHARMACEUTICAL

This invention relates to a novel pharmaceutical, to a process for the preparation of the pharmaceutical and to the use of the pharmaceutical in medicine.

International Patent Application, Publication Number WO2004/056369 discloses certain benzazepine derivatives including 6-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yloxy)-N-methyl-nicotinamide.

It has now been discovered that 6-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yloxy)-N-methyl-nicotinamide hydrochloride exists in a novel polymorphic form which is stable and does not exhibit significant hygroscopicity.

The novel polymorphic form ('the polymorph') has useful pharmaceutical properties and in particular it is indicated to be useful for the treatment and/or prophylaxis of neurological, psychiatric, sleep and gastrointestinal disorders, pain, epilepsy and obesity.

Accordingly, the present invention provides a polymorphic form of 6-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yloxy)-N-methyl-nicotinamide hydrochloride characterised in that it:

i) provides X-ray powder diffraction (XRPD) spectra comprising the following peaks at 5% or greater relative intensity:

Diffraction angle (°2θ)	Lattice spacing (Å)
4.6	19.2
9.2	9.6

; and/or

ii) has an onset of melting in the range 233-240°C, as measured by DSC.

In one aspect, the polymorph provides X-ray powder diffraction (XRPD) spectra comprising the following peaks at 5% or greater relative intensity:

Diffraction angle (°2θ)	Lattice spacing (Å)
4.6	19.2
9.2	9.6
13.8	6.4
18.4	4.8
20.4	4.4
20.5	4.3
20.8	4.3
21.3	4.2
22.1	4.0

25.0	3.6
29.6	3.0
29.7	3.0

More particularly, the polymorph provides an X-ray powder diffraction (XRPD) pattern substantially in accordance with Figure 1.

In another aspect, the polymorph has an onset of melting in the range 233-240°C, a peak max melting temperature in the range of 238-242°C and an enthalpy of melting in the range of 103-115 J/g. More particularly, the polymorph has an onset of melting in the range 233-240°C, a peak max melting temperature of approximately 241°C, and an enthalpy of melting of approximately 115J/g as measured by DSC. More particularly, the polymorph has an onset of melting in the range 233-240°C, a peak max melting temperature of 241°C, and an enthalpy of melting of 115J/g as measured by DSC.

In a more particular aspect, the polymorph provides a DSC thermogram substantially in accordance with Figure 2.

In a further aspect, the polymorph provides a TGA thermogram substantially in accordance with Figure 3.

The XRPD, DSC and TGA characterising data mentioned above is collected as described more fully in the section entitled "Characterising Data".

The present invention encompasses the polymorph isolated in pure form or when admixed with other materials, for example other salts or solvates (inclusive of their polymorphs) of 6-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yloxy)-N-methyl-nicotinamide, or any other material.

Thus in one aspect there is provided the polymorph in isolated or pure form. "Isolated" or "pure" form refers to a sample in which the polymorph is present in an amount of >75%, particularly >90%, more particularly >95% and even more particularly >99% relative to other compounds or polymorphs of 6-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yloxy)-N-methyl-nicotinamide hydrochloride which may be present in the sample.

The invention also provides a process for preparing the polymorph, characterised in that a solution of 6-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yloxy)-N-methyl-nicotinamide in methanol is treated with one equivalent of a chloride source, such as acetyl chloride, hydrogen chloride in diethylether or concentrated hydrochloric acid, followed by crystallisation with, for example, at least 1.5 volumes

ethyl acetate. In the above-mentioned process the solution may be seeded with the polymorph to induce crystallisation but this is not essential.

6-(3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yloxy)-N-methyl-nicotinamide may be prepared according to known procedures, such as those disclosed in WO2004/056369. The disclosure of WO2004/056369 is incorporated herein by reference.

As mentioned above the polymorph of the invention has useful therapeutic properties. More particularly, the compound of the present invention is believed to be of potential use in the treatment of neurological diseases including Alzheimer's disease, dementia (including Lewy body dementia and vascular dementia), age-related memory dysfunction, mild cognitive impairment, cognitive deficit, epilepsy, migraine, Parkinson's disease, multiple sclerosis (including fatigue), stroke, pain of neuropathic origin (including neuralgias, neuritis and back pain), inflammatory pain (including osteoarthritis, rheumatoid arthritis, acute inflammatory pain and back pain) and sleep disorders (including hypersomnolence, excessive daytime sleepiness, narcolepsy, sleep deficits associated with Parkinson's disease and fatigue, especially in multiple sclerosis); psychiatric disorders including psychotic disorders (such as schizophrenia (particularly cognitive deficit of schizophrenia) and bipolar disorder), attention deficit hypereactivity disorder, depression (including major depressive disorder), anxiety and addiction; and other diseases including obesity and gastro-intestinal disorders.

Accordingly, in one aspect, the present invention provides the polymorph for use as a therapeutic substance. More particularly, the invention provides the polymorph for use as a therapeutic substance in the treatment or prophylaxis of the above disorders, in particular cognitive impairments in diseases such as Alzheimer's disease and related neurodegenerative disorders.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of the polymorph.

In another aspect, the invention provides the use of the polymorph in the manufacture of a medicament for use in the treatment of the above disorders.

When used in therapy, the polymorph is usually formulated in a standard pharmaceutical composition. Such compositions can be prepared using standard procedures.

Thus, the present invention further provides a pharmaceutical composition for use in the treatment of the above disorders which comprises the polymorph and a pharmaceutically acceptable carrier.

The present invention further provides a pharmaceutical composition which comprises the polymorph and a pharmaceutically acceptable carrier.

The polymorph of the invention may be used in combination with other therapeutic agents. When the polymorph of the invention is intended for use in the treatment of Alzheimer's disease, it may be used in combination with medicaments claimed to be useful as either disease modifying or symptomatic treatments of Alzheimer's disease. Suitable examples of such other therapeutic agents may be symptomatic agents, for example those known to modify cholinergic transmission such as M1 muscarinic receptor agonists or allosteric modulators, M2 muscarinic antagonists, acetylcholinesterase inhibitors, nicotinic receptor agonists or allosteric modulators, 5-HT_4 receptor partial agonists, 5-HT_6 receptor antagonists or 5HT1A receptor antagonists and NMDA receptor antagonists or modulators, or disease modifying agents such as β or γ-secretase inhibitors.

When the polymorph of the invention is intended for use in the treatment of narcolepsy, it may be used in combination with medicaments claimed to be useful as treatments for narcolepsy. Suitable examples of such other therapeutic agents include modafinil, armodafinil and monoamine uptake blockers.

When the polymorph of the invention is intended for use in the treatment of schizophrenia, it may be used in combination with medicaments claimed to be useful as treatments of schizophrenia including i) antipsychotics including typical antipsychotics (for example chlorpromazine, thioridazine, mesoridazine, fluphenazine, perphenazine, prochlorperazine, trifluoperazine, thiothixine, haloperidol, molindone and loxapine), atypical antipsychotics (for example clozapine, olanzapine, risperidone, quetiapine, aripirazole, ziprasidone and amisulpride), glycine transporter 1 inhibitors and metabotropic receptor ligands; ii) drugs for extrapyramidal side effects, for example anticholinergics (such as benztropine, biperiden, procyclidine, and trihexyphenidyl) and dopaminergics (such as amantadine); iii) antidepressants including serotonin reuptake inhibitors (such as citalopram, escitalopram, fluoxetine, paroxetine, dapoxetine and sertraline), dual serotonin/noradrenaline reuptake inhibitors (such as venlafaxine, duloxetine and milnacipran), noradrenaline reuptake inhibitors (such as reboxetine), tricyclic antidepressants (such as amitriptyline, clomipramine, imipramine, maprotiline, nortriptyline and trimipramine), monoamine oxidase inhibitors (such as isocarboxazide, moclobemide, phenelzine and tranylcypromine), and others (such as buproprion, mianserin, mirtazepine, nefazodone and trazodone); iv) anxiolytics including benzodiazepines such as alprazolam and lorazepam; and v) cognitive

enhancers for example cholinesterase inhibitors (such as tacrine, donepezil, rivastigmine and galantamine).

When the polymorph is used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

The invention thus provides, in a further aspect, a combination comprising the polymorph of the invention together with a further therapeutic agent or agents.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When the polymorph of the invention is used in combination with a second therapeutic agent active against the same disease state the dose of the polymorph may differ from that when the polymorph is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising the polymorph of the invention and a sterile vehicle. The polymorph, depending on the

vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the polymorph can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the polymorph is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The polymorph can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the polymorph.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the polymorph, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.5 µg to 1mg, more suitably 0.5 to 500µg and even more suitably 1 to 50µg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

The following example illustrates the invention but does not limit it in any way.

Example 1: Preparation of the polymorph

6-(3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yloxy)-N-methyl-nicotinamide (4.0kg) and methanol (7.9kg) are charged to a reactor with stirring at 20 to 25°C for at least 30 minutes. Acetyl chloride (1.0kg) is added in methanol (7.9kg) at 0 to10°C and then slowly charged into the above reaction solution at 15 to 25°C. The reaction is then stirred at 45 to 55°C until reaction mixture becomes brown clear solution. The reaction solution is filtered hot and then vacuum concentrated at NMT 50°C to about 1/2 volume to afford white slurry mixture. Ethyl acetate (18.0kg) is slowly charged into the reaction solution at 45 to 55°C and then stirred at this temperature for at least 1 hour. The white slurry mixture is cooled to 15 to 25°C at ramping rate 10°C /hr and then stirred at this temperature NLT 24 hours. The slurry mixture is filtered, and the cake is washed by Ethyl acetate (3.6Kg x 2) twice to give the "wet cake" 6-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yloxy)-N-methyl-nicotinamide hydrochloride as a white solid (6.203 Kg).

The intermediate grade 6-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yloxy)-N-methyl-nicotinamide hydrochloride (6.203 Kg) and methanol (7.2 Kg) are charged into a reactor and then heated to 45 to 55°C. Ethyl acetate (17.7Kg) is slowly charged at 45 to 55°C, and then the solution is stirred at this temperature for at least 1 hour. The white slurry mixture is cool to 15-25°C for at ramping rate 10°C /hr and then stirred at this temperature NLT 24 hours. The slurry mixture is filtered, and the wet cake is washed with ethyl acetate (3.6Kg x 2). The product is vacuum dried at NMT 50°C to give the polymorph as a white solid (3.034 Kg, 77%th).

Example 2: Preparation of the polymorph

6-(3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yloxy)-N-methyl-nicotinamide (1wt, 2g) was slurried in Methanol (5 vol, 10ml) at room temperature. Conc. HCl (0.26 vol, 0.52ml) was added resulting in a solution. Methanol (ca 2.5 vols, 5ml) was removed by distillation at atmospheric pressure. The solution was cooled to just below reflux temperature before slowly adding ethyl acetate (7.5 vols, 15ml) to induce crystallisation. The mixture was allowed to cool to room temperature and stirred for 18hrs. The solids were collected by filtration and rinsed with ethyl acetate. The damp cake was dried at 50°C to give the polymorph.

Example 3: Preparation of the polymorph

A 1M solution of hydrogen chloride in diethylether (10.5 ml) was added to a stirring suspension of 6-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yloxy)-N-methyl-nicotinamide (3.5g, 10mM) in methanol (20 ml). A clear solution formed. The resulting mixture was stirred at room temperature for 60 min. The mixture was evaporated to give a pale yellow gum. This was suspended in ethyl acetate (100 ml) and heated to 100°C. Methanol (50 ml) was added and the mixture heated to reflux until a clear solution was obtained. The azeotrope was removed by evaporation until the mixture became turbid. The mixture was allowed to cool and the white solid collected by filtration. This was washed with ethyl acetate and dried in a vacuum oven at 40°C over the weekend to yield form 1 (2.48g).

Example 4: Recrystallisation of the polymorph

Two batches of 6-(3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yloxy)-N-methyl-nicotinamide hydrochloride (500mg) were each dissolved in ethanol (14 vols) at 75°C. The reaction mixtures were cooled to 15°C over 2 hours and then allowed to age at 15°C for 2 hours. The suspensions were left unstirred overnight at RT. The products were isolated by filtration, washed with ethanol and dried in vacuo at 40°C. Yields = 69 & 71%

CHARACTERISING DATA: The following characterising data were generated for the polymorph:

A. X-Ray Powder Diffraction (XRPD)

The XRPD pattern of the Polymorph is shown below in Figure 1 and a summary of the XRPD angles and calculated lattice spacings characteristic of the Polymorph is given in Table 1.

The sample was prepared using silicon wafer technique and the X-Ray Powder Diffraction (XRPD) analysis was performed on a PANalytical X'pert Pro powder diffractometer, Model PW3040/60 using an X'Celerator detector. The acquisition conditions were:

Radiation:	Cu K_α,
Generator tension:	40 kV
Generator current:	45 mA
Start angle:	2.0 °2θ
End angle:	40.0 °2θ
Step size:	0.0167 °2θ
Time per step:	31.75 seconds

Table 1: X-Ray Powder Diffraction Angles and Calculated Lattice Spacings Characteristic of the Polymorph.

Diffraction angle (°2θ)	Lattice spacing (Å)
4.6	19.2
9.2	9.6
13.8	6.4
18.4	4.8
20.4	4.4
20.5	4.3
20.8	4.3
21.3	4.2
22.1	4.0
25.0	3.6
29.6	3.0
29.7	3.0

B. Differential Scanning Calorimetry (DSC)

Figure 2 depicts a DSC thermogram of the polymorph recorded on a TA instruments Q1000. The sample was heated at 10 °C min^{-1} in a crimped aluminium pan with a pin-hole lid.

C. Thermogravimetric Analysis (TGA)

Figure 3 depicts a TGA thermogram of the polymorph recorded on a TA instruments Q500. The sample was heated at 10 °C min^{-1}.

PROPERTIES: The properties of the polymorph were tested as set out below:

A. Stability

The solid state stability of the polymorph was determined after storing for 4 weeks in closed containers at 40°C and 50°C, and after open exposure to heat and humidity - 40°C/75% Relative Humidity (referred to as 40°C/75%RH (O) hereafter).

After the samples were removed from store, solutions were prepared and analysed by gradient HPLC. The conditions used are shown below.
Sample solutions were prepared at a concentration of approximately 0.05mg/mL in a suitable solvent (90:10 v/v pH3 phosphate buffer (0.05M NaH_2PO_4 adjusted to pH3 with H_3PO_4): acetonitrile). Unstressed material was prepared in the same way to act as the standard.

Chromatographic conditions.
HPLC Equipment: Waters Alliance HPLC system (or suitable equivalent).

Gradient profile		
Time (minutes)	0.05% v/v trifluoroacetic acid in water	0.05% v/v trifluoroacetic acid in acetonitrile
0	100	0
8	5	95
8.1	100	0
10	100	0

The gradient change for the period 0 to 8 minutes was linear.
Flow rate = 1mL/min.
Column: Phenomenex LUNA C18(2) 3u, 50mm by 2mm
Column Temperature: 40°C
Detection: UV at wavelength of 240nm.
10uL aliquots injected.
Other suitable conditions may be used for analysis.
Chromatograms were recorded and analysed using Turbochrom software (other suitable equivalent systems, e.g. Empower may also be used).

The chromatograms of the samples were compared with those of solutions of the initial material (standard). The calculated polymorph content of the samples was performed by comparing the peak areas produced for the polymorph peak of the standard (unstressed material) with those observed in the samples with consideration of the weight taken. The calculation can be depicted as:
Standard response was calculated by dividing the concentration (expressed as the free base) by the polymorph peak area observed in the chromatogram. This was repeated a number of times to get an average response. A second standard was prepared to check the accuracy of the first standard and typically the agreement between the two standards would be within ±1%.

The polymorph content of the samples is calculated by multiplying the average standard response by the polymorph peak area observed in the chromatogram and then multiplying this value by the volume of solution made up to get a calculated weight. This weight is then divided by the actual weight taken and multiplied by 100 and multiplied by a correction factor (to convert from free base to the hydrochloride salt) to get the polymorph content expressed as a percentage.

The related substances value was obtained by totaling up all of the observed peaks related to polymorph to get total A. Any individual peaks observed were divided by total A and multiplied by 100 to get a % normalized peak area of the peak(s). If a sample consists of only one peak which was due to polymorph (i.e. no related substance was observed), this results in a 100% normalized peak area.

Results

Table 2 shows the calculated polymorph content of the solid samples.

Table 3 shows the calculated related substances (degradation profile) of the solid samples.

Table 2

Sample	Polymorph content (%w/w)
50°C	99.6
40°C/75%RH (O)	100.0
40°C	99.8

Table 3

Sample	% Normalised Peak Area of observed peaks (Relative Retention Time =1.00)
Standard	100.00
50°C	100.00
40°C/75%RH (O)	100.00
40°C	100.00

CLAIMS:

1. A polymorphic form of 6-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yloxy)-N-methyl-nicotinamide hydrochloride characterised in that it:

i) provides X-ray powder diffraction (XRPD) spectra comprising the following peaks at 5% or greater relative intensity:

Diffraction angle (°2θ)	Lattice spacing (Å)
4.6	19.2
9.2	9.6

; and/or

ii) has an onset of melting in the range 233-240°C, as measured by DSC.

2. A polymorphic form of 6-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yloxy)-N-methyl-nicotinamide hydrochloride according to claim 1 which provides an X-ray powder diffraction (XRPD) spectra comprising the following peaks at 5% or greater relative intensity:

Diffraction angle (°2θ)	Lattice spacing (Å)
4.6	19.2
9.2	9.6
13.8	6.4
18.4	4.8
20.4	4.4
20.5	4.3
20.8	4.3
21.3	4.2
22.1	4.0
25.0	3.6
29.6	3.0
29.7	3.0

3. A polymorphic form of 6-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yloxy)-N-methyl-nicotinamide hydrochloride according to claim 2 which provides an X-ray powder diffraction (XRPD) pattern substantially in accordance with Figure 1.

4. A polymorphic form of 6-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yloxy)-N-methyl-nicotinamide hydrochloride according to claim 1, wherein the polymorph has an onset of melting in the range 233-240°C, a

peak max melting temperature in the range of 238-242°C and an enthalpy of melting in the range of 103-115 J/g, as measured by DSC.

5. A polymorphic form of 6-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yloxy)-N-methyl-nicotinamide hydrochloride according to claim 4, which provides a DSC thermogram substantially in accordance with Figure 2.

6. A polymorphic form of 6-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yloxy)-N-methyl-nicotinamide hydrochloride according to claim 1 which provides a TGA thermogram substantially in accordance with Figure 3.

7. A pharmaceutical composition which comprises a polymorphic form as defined in any one of claims 1 to 6 and a pharmaceutically acceptable carrier or excipient.

8. A polymorphic form as defined in any one of claims 1 to 6 for use in therapy.

9. A polymorphic form as defined in any one of claims 1 to 6 for use in the treatment of neurological diseases.

10. Use of a polymorphic form as defined in any one of claims 1 to 6 in the manufacture of a medicament for the treatment of neurological diseases.

11. A method of treatment of neurological diseases which comprises administering to a host in need thereof an effective amount of a polymorphic form as defined in any one of claims 1 to 6.

12. A pharmaceutical composition for use in the treatment of neurological diseases which comprises a polymorphic form as defined in any one of claims 1 to 6 and a pharmaceutically acceptable carrier.

13. A process for the preparation of a polymorphic form as defined in claim 1, which process comprises treating a solution of 6-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yloxy)-N-methyl-nicotinamide in methanol with one equivalent of a chloride source, followed by crystallisation with at least 1.5 volumes ethyl acetate.

Application No:	GB0618135.8	**Examiner:**	Stephen Quick
Claims searched:	1-13	**Date of search:**	14 January 2008

Patents Act 1977: Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance
A	-	Journal of Pharmacology and Experimental Therapeutics, 2007, Vol. 321(3), pages 1032-1045. See references to GSK189254, namely to definition (page 1032, abstract, 1st sentence) & preparation (page 1033, RH column, 3rd complete paragraph, 1st sentence).
A	-	WO 2004/056369 A1 (GLAXO GROUP). See examples 121 (pages 47-48, all three variants); acknowledged in this application.
A	-	WO 2006/072596 A1 (GLAXO GROUP). See examples 1 & 2.
A	-	WO 2005/014479 A2 (GLAXO GROUP). See examples 26 & 27.

Categories:

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC^{X} :

Worldwide search of patent documents classified in the following areas of the IPC

The following online and other databases have been used in the preparation of this search report

CAS ONLINE

International Classification:

Subclass	Subgroup	Valid From
C07D	0401/12	01/01/2006
A61K	0031/55	01/01/2006

Subclass	Subgroup	Valid From
A61P	0001/00	01/01/2006
A61P	0003/04	01/01/2006
A61P	0007/02	01/01/2006
A61P	0009/10	01/01/2006
A61P	0019/02	01/01/2006
A61P	0025/00	01/01/2006
A61P	0025/06	01/01/2006
A61P	0025/08	01/01/2006
A61P	0025/16	01/01/2006
A61P	0025/18	01/01/2006
A61P	0025/22	01/01/2006
A61P	0025/24	01/01/2006
A61P	0025/28	01/01/2006
A61P	0025/30	01/01/2006
A61P	0029/00	01/01/2006